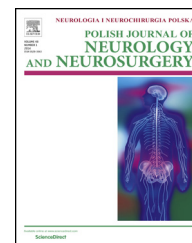


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## Review article

## Alternating hemiplegia of childhood: New diagnostic options

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## ABSTRACT

A syndrome of alternating hemiplegia of childhood (AHC) is a rare disorder first presented in 1971. AHC is characterized by transient episodes of hemiplegia affecting either one or both sides of the body. Age of onset is before 18 months and the common earliest manifestations are dystonic or tonic attacks and nystagmus. Hemiplegic episodes last minutes to days and the frequency and duration tend to decrease with time. Motor and intellectual development is affected, deficits may also develop later. Epileptic seizures occur in some patients. Neuroimaging of the brain usually reveals no abnormalities. The variability of individual clinical presentations and evolution of symptoms have made diagnosis difficult. Therefore the problems of misdiagnosis could account for the low prevalence of this syndrome. This paper hopes to present actual data on AHC, especially of the results of genetic research and new diagnostic tools.

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## 1. Introduction

Alternating hemiplegia of childhood (AHC, MIM 104290) was presented by Verret and Steel in 1971 [1]. Alternating hemiplegia of childhood is a rare syndrome with an early manifestation, and its diagnosis is based on the clinical symptoms fulfilling the criteria. The incidence has been estimated at 1 in 1000,000 births but the underestimation of the burden of AHC could be suspected due to the lack of sufficient knowledge about this syndrome or lack of diagnostic laboratory or radiological test confirming diagnosis with certainty [2]. Until recently, no hypothesis explaining AHC pathomechanism has been confirmed. Although in single cases pathological changes were detected suggesting vasculitis or mitochondrial enzymatic chain disorders, specific marker of the disease was not defined. The phenotypic features common with migraine (hemiplegia as

a symptom of motor migraine aura) suggested that AHC constitutes migraine precursor or variant of hemiplegic migraine (FHM, familial hemiplegic migraine). Majority of presented cases were predominantly sporadic, however familial cases with transmission suggesting autosomal dominant trait were presented [3,4].

Multicenter research on AHC pathomechanism succeeded with the identification of ATP1A3 mutation. The research was conducted in collaboration with European Network for Research on Alternating Hemiplegia (ENRAH), an organization including patients and their families as well as clinicians to help coordinate epidemiological data and to promote research efforts [5,6].

The translation of the name of the syndrome into Polish was not unified. In the publication of the Polish version of the International Classification of Headache Disorders 'alternating plegia of childhood' (*naprzemienne porażenie dziecięce*) was

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presented in a section of childhood periodic syndromes that are commonly precursors of migraine [7]. A case of a patient hospitalized at the Department of Developmental Neurology AM in Gdańsk was presented in 1976 as 'alternating hemiplegia in a child' [8]. The next case of a girl with AHC hospitalized at the Department of Neurology of Polish Mother's Memorial Research Institute Hospital (Centrum Zdrowia Matki Polki) in Łódź was described in 1995 as 'alternating hemiplegia' [9]. The term 'alternating hemiplegia of childhood' was applied in the paper related to the significance of neuronal channelopathies in the pathogenesis of migraine [10].

## 2. The classical course of AHC

In majority of children diagnosed with AHC, regardless of climatic region, the key symptom, namely hemiplegia occurred before 18 months of life. A plegia usually occurs during following attacks at alternating body sides. Sometimes, however, it begins unilaterally but later evolves to bilateral hemiplegia or transfers to the opposite side of the body during one attack. Bilateral plegia since the beginning of attacks was also observed during some episodes. Deterioration of consciousness was not associated with episodes of hemiplegia. Involuntary movements, including facial dyskinesia, dystonia and athetosis were associated with hemiplegia or occurred independently. In AHC cases manifesting during first days of life, ocular movement disorders or involuntary movements are the first to occur [11]. Later on, cerebellar ataxia appeared also with the disease's progression. Headaches were reported by 58% of children with AHC, although migraine with aura was diagnosed in 16% [12]. Epileptic seizures were not in a close time relation to hemiplegic episodes, but in some cases hemiplegia could be incorrectly diagnosed as Todd palsy. In majority of children, symptoms resolved during sleep, they appeared however during prolonged attacks 10–20 min after awakening [13–15].

Diagnostic criteria of AHC are presented in Table 1 [13,14]. The criterion of immediate disappearance of all symptoms while going to sleep was not always included as necessary to establish diagnosis of AHC in retrospective research, since responses in questionnaires did not contain such precise data [15]. The early clinical signs recognized as most convincing for diagnosis of AHC in infants included episodic nystagmus, especially monocular [11]. Table 2 provides data related to most important episodic AHC symptoms, especially most

**Table 1 – Diagnostic criteria for alternating hemiplegia of childhood.**

1. Onset before age of 18 months
2. Repeated episodes of hemiplegia involving alternating body sides
3. Episodes of bilateral hemiplegia or quadriplegia, starting bilaterally as separate attack or as generalization of a hemiplegic episode
4. Disappearance of all symptoms upon sleeping
5. Other paroxysmal disturbances, including dystonic spells, abnormal oculomotor symptoms or autonomic phenomena occurring during hemiplegic spells or independently
6. Evidence of developmental delay or neurologic abnormalities, including choreoathetosis, dystonia, or ataxia

early symptoms: abnormal ocular symptoms and dystonia. In relation to hemiplegia, which occurs in 100% of examined patients, only the mean age of onset was presented. Table 3 shows data for most common non-episodic symptoms. The table contains the year of paper's publication, the duration of the research, and also the age of children at the time of diagnosis [11,16,17]. There is a tendency for earlier AHC diagnosis in younger patients. The data presented in papers listed in references is more precise than included in tables. The paper of Sweney et al. presents results of observations, that episodic abnormal ocular movements were documented in 93% of patients, within 83% during first 3 months of life, but in 32% in first 2 days of life. Such information may have a significant impact on the early AHC diagnosis [4].

## 3. Stages of the course of AHC

Authors of the research on AHC noticed changes in clinical symptoms with the age of children [4,11]. Mikati et al. [15] proposed three phases of symptoms evolution in AHC patients. These phases do not mean the constant deterioration of development of patients but rather fluctuations in their condition. Stage I lasts for about one year and manifests itself during first months of life with episodic abnormal ocular movements, such as horizontal, vertical or rotatory nystagmus, which can be also unilateral, gaze deviation to one side or upwards, paralysis of conjugate gaze, loss of convergence or convergent strabismus. Abnormal ocular movements were the first to occur in 83% of patients, as a presenting symptom [4].

**Table 2 – Review of age of symptoms onset (months) and prevalence of episodic symptoms in patients with alternating hemiplegia of childhood.**

Author	Group	Age of hemiplegia onset (months); mean	Oculomotor abnormalities		Dystonia (%)	Epilepsy (%)
			Age (months); mean	%		
Panagiotakaki et al. [12]	157	7	ND	91	88	53
Sweney et al. [4]	103	6.6	2.4	93	83	41
Mikati et al. [15]	44	<18 (84%) >18 (16%)	ND	100	95	18
Silver et al. [16]	10	9	ND	ND	ND	50
Saito et al. [17]	9	8	3.2	100	89	77.7
Nevsimalová et al. [11]	8	16.3	4.1	ND	ND	87.5

ND – no data available.

**Table 3 – Review of age of children at the time of diagnosis (months) and prevalence of symptoms significant for diagnosis of alternating hemiplegia of childhood.**

Author, year of publication	Research duration	Age at time of diagnosis (months); mean	Developmental delay (%)	Ataxia (%)
Panagiotakaki et al. (2010) [12]	2005–2007	20	92	ND
Sweney et al. (2009) [4]	1998–2007	36	100	96
Mikati et al. (2000) [15]	1995–2000	40	91	68
Silver et al. (1993) [16]	ND	52	88.8	ND
Saito et al. (2010) [17]	ND	ND	100	ND
Nevsimalová et al. (2005) [11]	ND	33	100	ND
ND – no data available.				

The earliest AHC manifestation, in the neonatal period, was reported in 12.5% of examined patients not only as oculomotor dysfunction, but also as involuntary movements including dystonia, changes of behaviour or dysfunction of autonomic nervous system [12,15]. Mild developmental delay was closely associated with episodic symptoms [11,15].

During stage II, lasting for 1–5 years, patients began to have hemiplegic spells, usually about 5 months after first AHC symptoms. However if hemiplegia had occurred earlier (in 32% of patients as the first symptom) than during this phase, the hemiplegic spells became more frequent [15]. After the incomplete recovery from hemiplegic spells, patients usually achieved the ability of independent walking between 12 and 60 months of life. The gait was affected, by involuntary movements, cerebellar ataxia and hypotonia persistent between hemiplegic spells. Movement disorders influenced also fine motor skills, resulting in clumsiness [4,11]. Encephalopathy with or without associated movement disorders was recognized in 92–100% of patients, and in 20% of patients even before the onset of typical symptoms of AHC. In other patients, a loss of already acquired skills, called milestones of development was observed [4,15]. Gross motor abnormalities were diagnosed in 84% of children younger than 2 years [12].

Epilepsy manifested itself usually between second and sixteenth year of life. A single seizure attack occurred in 53% of the patients, and recurrent attacks were experienced by 18–47% of the patients, as partial or partial with secondary generalization [12,15]. Several types of epileptic seizures were observed, including tonic-clonic, myoclonic and gelastic. Usually seizures were not in close time relation to hemiplegic spells. Status epilepticus of partial seizures was also reported [12,15]. Epilepsy was relatively well controlled with medication. Dystonic spells were, however, resistant to antiepileptic treatment, and electroencephalography performed during attack did not register any epileptical patterns. Unfortunately, in the case of hemiplegic episodes, an incomplete data resulted in interpretation of hemiplegia as postictal one and drug-resistant epilepsy was diagnosed [4,15,16].

During stage III, deficits were persistent, with aphasia and intellectual disability affecting school performance. With maturation of the nervous system, hemiplegic spells became less common but remission was incomplete and paresis persisted in form of hemiplegia, tetraplegia, paraplegia or diplegia. The course of the disease is unpredictable and fluctuating [15,16]. The death reported in 3–4% of patients was caused by status epilepticus, severe plegia of limbs, cardiorespiratory insufficiency or dysfunction of the autonomic nervous system [4,12].

#### 4. The characteristics of hemiplegia

Premonitory signs prior to paroxysmal phenomena were reported by 41% patients. The common associated with hemiplegia symptoms were headaches in half of the patients, mood disorders in 37% and vomiting in 10% of the patients. Sensory phenomena involving hands and feet were also reported. Premonitory phase may also consist of an alteration in mental state with screaming, irritability or behavioral changes [12,15]. Sudden and unexpected onset of hemiplegia was also observed but always during awake stage with hyperventilation or autonomic dysfunction [16,17]. In one of presented cases, hemiplegia was precipitated by fever and partial secondary generalized seizures [18]. Hemiplegia manifested itself in half of the cases at about 6 months of age and lasted between few minutes and 14 days. Hemiplegic spells recurred with varying frequency, in the most severe cases several times during the same day [18]. The triggering factor was excitement, stress, tiredness, trauma, bright light, heat, cold or a bath. In one patient, hemiplegia could be triggered by induced crying, which was a precipitating factor in young children [19,20]. Tetraplegia, especially flaccid, was the least common plegia type, causing not only immobilization of patients but also speech problems (mainly dysarthria), swallowing problems, and occasionally respiratory problems including respiratory insufficiency in most severe cases [17]. Speech problems were observed only during right-sided hemiplegic spells [12]. Deep tendon reflexes were absent in majority of examined patients but in some patients brisk deep tendon reflexes and Babinski sign were detected. Other characteristic features of hemiplegia were fluctuations in its severity. Hemiplegia occurred more commonly in one side of the body, but was more severe at the opposite body side [15].

Hemiplegic spells were accompanied by symptoms of autonomic nervous system dysfunction and the most typical were skin color changes, paleness, flushing or sometimes cyanosis, changes of pupil's diameter (myosis or mydriasis), vomiting, diarrhea, sweating or the increase of body temperature [3,15,21].

#### 5. AHC symptoms in adults

Since AHC was diagnosed in children, attention was also paid to family members well-being. In a mother of one patient, mild cognitive disorders were detected, and a broad-based gait.

History revealed two episodes of generalized tonic-clonic seizures during childhood (when she was 4 and 10 years old), and dysarthria during pregnancy. Her hemiplegic spells, observed since she started to walk, lasted for minutes to 2 h, with decreasing frequency. The mother's uncle suffered from alternating hemiplegia of limbs or unusual limbs posturing, recurrent since his childhood but medical help was not requested [18].

In 34 out of a group of 37 adults with AHC, the data on employment status was available. Only one person was able to work independently and the other 13 worked with assistants [12].

## 6. Non-typical AHC cases

Sporadic AHC cases were reported with unusually mild course. The onset was late and dystonic spells were more pronounced than hemiplegic, and also the psychomotor development of children was good. Contrary, in some patients the course of AHC was severe, with atrophy of optic nerves atrophy or hypoacusis [11,15,21]. Unusual AHC course caused the exclusion of children from research group [4].

## 7. Differential diagnosis

Spectrum of clinical symptoms of AHC is broad, what makes differentiated diagnosis difficult. The progressive diseases must be excluded, with the special attention to treatable conditions. This is especially difficult in young children, when clinical manifestation is incomplete. Causes of acute hemiplegia in children are presented in Table 4 [4,11,16,17]. These were specifically included among the most important causes presented by Tenney et al. [14].

One of the disorders worth mentioning in the differential diagnostics is benign nocturnal alternating hemiplegia of childhood (BNAH), significantly different from classic, severe AHC. Typically, hemiplegic spells occurred during sleep, and they were preceded by crying, rendering affection of parents. Patients were conscious, sometimes agitated, they, however, did not have involuntary movements or abnormal ocular movements, and their psychomotor development was not affected. The trait of transmission was also different, associated with chromosome X. Benign nocturnal alternating hemiplegia of childhood should be differentiated from hemiplegic migraine, frontal lobe epilepsy, rolandic epilepsy, Panayiotopoulos syndrome and sleep disorders [22,23].

## 8. Diagnostic tests

The identification of ATP1A3 mutation in AHC patients was the diagnostic turning point [5,6]. Despite the availability of this new diagnostic tool allowing AHC confirmation, it is still necessary to use clinical criteria. Additional tests serve only to exclude other diseases causing alternating hemiplegia [15,21]. Individually, results of different tests were incorrect, however, none were informative or characteristic enough to serve as a tool to confirm AHC. The examples of commonly

**Table 4 – Differential diagnosis of acute hemiplegia in children.**

Stroke
Vascular dysplasia: moyamoya, artery dissection
Hematologic disorders, coagulopathies, antiphospholipid antibody syndrome
Cardiac muscle diseases, embolism
Vasculitis, connective tissue disorders
Metabolic diseases
MELAS, pyruvate dehydrogenase deficiency
Congenital disorders of glycosylation, homocystinuria
Neuromuscular diseases
Polio-like syndrome
Compression neuropathy
Epilepsy
Postictal paralysis, Rasmussen syndrome
Migraine
Familial hemiplegic migraine
Alternating hemiplegia of childhood
MELAS – mitochondrial encephalopathy, lactic acidosis, stroke-like episodes.

performed tests according to Sweney et al. [4] were presented, in Table 5. Results of neuroradiological tests were normal in most cases, and only in single patients, especially severely affected or older, changes were detected, including cerebellar atrophy, polymicrogyria, syringomyelia or hippocampal pathology [11,24]. Normal results were achieved in laboratory tests, including ammonia, creatine kinase, mucopolysaccharides, lysosomal enzymes and very long chain fatty acids [21,25]. Some functional tests allowed registration of pathological changes occurring during hemiplegic spells in patients. Single-photon emission computed tomography detected hypoperfusion of the hemisphere contralateral to

**Table 5 – Methods of evaluation in determining the diagnosis of alternating hemiplegia of childhood (AHC).**

Method	Goal
Magnetic resonance, magnetic resonance angiography, spectroscopy of magnetic resonance	To exclude structural central nervous system abnormalities (stroke, metabolic disorders) or vasculopathies
Cerebrospinal fluid examination: glucose, lactic acid and pyruvate, neurotransmitters, metabolites of pterins, folates, amino acids	To exclude disorders of dopamine synthesis or disorders associated with pyridoxine or folates deficiency
Metabolic screening tests of blood and urine	To exclude mitochondrial disorders, glucose-transporter-deficiency, organic acidurias or carnitine deficiency
Thyroid gland examination	To exclude periodic paralysis associated with hyperthyroidism
Video EEG (12-24-h monitoring)	Registration of epileptic seizures and non-epileptic attacks
Genetic tests: ATP1A3 CACNA1A, ATP1A2, SLC1A3	To confirm AHC Differential diagnosis (AHC and FHM)



hemiplegia, followed by hyperperfusion [15]. Those changes were similar to dysfunction detected already in patients with migraine but different from that seen in epilepsy. Positron emission tomography revealed a decrease of glucose metabolism in the brain (frontal region) or cerebellum in some patients during interictal period [4,12,15].

Magnetic resonance spectroscopy of skeletal muscle at rest and after exercise revealed the presence of changes resembling mitochondrial dysfunction. However, results of muscle biopsy performed in individual patients did not suggest significant changes, with non-specific increase in lipid content or mitochondrial enzyme activity changes [25,26]. Skin biopsy, performed in few patients, revealed the presence of cytoplasmatic vacuoles and also apoptosis in vascular smooth muscle cells indicating similarities between AHC and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Changes in MMP-9 (matrix metalloproteinase-9), TIMP-1 (tissue inhibitor MMP-1), were not specific for AHC – they could reflect vasogenic changes, detected sometimes in patients with migraine. The casual relation of migraine and ischaemic stroke is still unclear. The levels of SP (substance P) and CG-RP (calcitonin gene-related peptide) in AHC patients were different than in patients with migraine, suggesting that trigeminovascular theory does not apply to AHC. Changes in SP may reflect dysfunction of autonomic nervous system in AHC patients [27-29].

## 9. Genetics and pathomechanism of AHC

ATP1A3 mutations were likely to be responsible for at least 74% of AHC cases, causing reductions in ATPase activity. None of the mutations known to cause rapid-onset dystonia-parkinsonism was found in patients with AHC [6]. The ATP1A2 mutation was described earlier in patients with FHM associated with benign familial infantile seizures and also in a child with overlapping AHC and FHM symptoms [30,31]. *De novo* CACNA1A mutation was proved in monozygotic twins with phenotype indicating a co-existence of FHM and atypical AHC [32]. One family was also reported with AHC symptoms in proband and other family members and also with the balanced translocation 46, XY, t(3;9)(p26;q34); the same mutation, however, was discovered in asymptomatic family member [30]. Although in children with AHC the decrease of glucose level was not detected in the cerebrospinal fluid (CSF), mutation of GLUT-1 was reported in one child presenting AHC phenotype. In a classical syndrome of Glut1 deficiency, signs and symptoms such as epilepsy, retardation of psychomotor development, spasticity, speech disorders, dystonia and secondary microcephaly were usually observed [33,34].

## 10. AHC therapy

The majority of drugs given to patients diagnosed with AHC since a syndrome was described, were ineffective. The best therapeutic results were achieved with flunarizine, which became a drug of choice. In some patients, flunarizine caused the reduction of frequency, time and severity of hemiplegic

spells but the effect was sometimes transient and satisfactory only during first stage of treatment. Nevertheless, after therapy termination, exacerbation of disease was observed. Although studies were not randomized and groups of patients were small, the effectiveness of this drug in the prophylactic treatment of patients with AHC is still reported. In AHC patients, in whom flunarizine was not effective since the beginning (non-responders), other medication was applied, including amantadine or acetazolamide [27]. The acute management of attacks is difficult; several drugs given to abort hemiplegic spells were partially effective, including chloral hydrate, diazepam or lorazepam. Neuroleptics, propranolol, carnitine and coenzyme Q were ineffective in AHC patients, and aripiprazole was reported as helpful only in one case. Epilepsy was not drug-resistant in majority of patients with AHC. Antiepileptic drugs were mostly ineffective to treat symptoms other than seizures. Topiramate was the only drug able to influence the severity of AHC in some patients [35].

## 11. Prognosis

The clinical course of AHC was more severe in sporadic cases than in familial ones. Prognosis was significantly influenced by the age of onset, and especially early occurring hemiplegic spells [13]. The development of children with neonatal-onset manifestation was severely affected. Recurrent convulsive status epilepticus led to deterioration of psychomotor development [16]. Although in some children motor dysfunctions caused wheelchair-dependency, other patients were able to lead independent life in adulthood. With maturation, hemiplegic spells, as well as abnormal ocular movements were less common also hypotonia was less severe. The natural AHC course was fluctuating and unpredictable, and in the long period of time until adulthood, the progression was not always seen. For this reason, the existence of AHC subtypes cannot be excluded [12,17,21].

The newest achievement of research in the field of AHC genetics was the identification of ATP1A3 mutation, presented during 12th International Child Neurology Congress and published in *Nature Genetics* and *Lancet Neurology* in 2012 [5,6]. The possibility of disease confirmation opens new perspectives, and new field of research, including clinical and epidemiological ones.

## Conflict of interest

None declared.

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## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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